Office Action Summary	Application No.	Applicant(s)	
	10/647,654	INGHAM ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,11-13,23-26 and 42-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 6, 11-13, 23-26, 42-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 4/26/2007have been entered in full. Applicant is notified that any outstanding rejection or objection that is not maintained in this Office action has been withdrawn.

Claims 1-3, 5, 6, 11-13, 23-26, 42-56 are pending. Further, the claims will be examined only to the extent that they read on *in vivo* methods of modulating neural cells with sonic hedgehog polypeptides and as the claims may read on anoxia induced ischemia, as set forth previously. It is noted that Applicant requests clarification regarding the species election; as set forth in the restriction requirement of 6/26/2007, upon the allowance of a generic claim, applicant will be entitled to consideration of additional species which depend from or otherwise require all the limitation of an allowable generic claim as provided by 37 CFR1.141.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 23, 25, 26, 29, 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require the term "hedgehog polypeptide" without reference to specific amino acid sequences are indefinite because the instant specification does not identify that material element or combination of elements which is unique to, and therefore, definitive of "hedgehog polypeptide". An artisan cannot determine what limitations are placed upon a claim by the presence of this term.

Applicant argues that the specification provides examples, as well as structural and functional features of hedgehog polypeptides. This argument has been fully considered but not deemed persuasive. The specification does not define hedgehog polypeptides as requiring any particular structure or function and nor are the examples sufficient to describe what is and what is not a hedgehog polypeptide.

Additionally claim 25 requires a "bioactive" fragment which the specification refers to as a fragment of a hedgehog polypeptide, wherein the encoded polypeptide specifically agonizes or antagonizes inductive events mediated by wild-type hedgehog proteins. The hedgehog bioactive fragment preferably is, for example, at least 5, 10, 20, 50, 100, 150 or 200 amino acids in length. However, the specification has not established what are and are not "inductive events mediated by wild-type hedgehog proteins", thus the skilled artisan could not be reasonably sure that he or she were practicing the claimed invention.

Applicant argues that it is not necessary to for the specification to list all of the specific induction events of hedgehog proteins because they are all well known in the art. This argument has been fully considered but not deemed persuasive. The art recognizes that there are many diverse and disparate induction events caused by the many different hedgehog proteins. The specification does not assert that any particular induction event is required and nor that all are.

Thus, one skilled in the art would not know whether the use of a particular fragment was within the bounds of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 6, 11-13, 23-26, 42-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of promoting growth, differentiation and/or survival of embryonic neuronal cells by administering a polypeptide (sonic hedgehog) of SEQ ID NO: 8, 11, 12, and 13 or an N-terminal autoproteolytic portion thereof (as described in the specification), does not reasonably provide enablement for administering a polypeptide other than a polypeptide of SEQ ID NO: 8, 11, 12, and 13, nor for the administration of portions of the polypeptides other than that of the N-terminal autoproteolytic portion, and nor does the specification provide enablement for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells, e.g. treating an neurodegenerative disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims encompass methods of promoting one or more of growth, differentiation and survival of adult neuronal cells in culture. The specification provides that neuronal cells grown in culture, including those from adult tissue, readily lose their differentiated state (see page 59, line 18). Also, the specification puts forth that hedgehog proteins can be added to cultures of cells in order to maintain the integrity of a culture of terminally differentiated neuronal cells by

preventing loss of differentiation (see page 59, lines 22-25). Additionally, the specification provides examples of the use of sonic hedgehog in the promotion of growth, differentiation, and survival of embryonic neuronal cells. It is known that sonic hedgehog is endogenously expressed in embryos, and one of skill in the art would therefore expect that embryonic tissues would be responsive to sonic hedgehog. However, the specification also discloses experiments that indicate sonic hedgehog is not expressed in adult tissues (see page 110, lines 10-11). One of skill in the art would therefore expect that adult tissues would not be responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Therefore, one of skill in the art would be required to perform undue trial and error experimentation in order to determine which of the multitude of adult neural cells is responsive to sonic hedgehog. Furthermore, Triffort et al., Journal of Neurochemistry 70(1327-1330)1998, describe the state of the art as follows: "The roles of HH signaling in adult vertebrates have been poorly documented so far, particularly in the brain where Ptc and Smo transcripts have been identified", see the last paragraph of col 1 of page 1327. Thus, even if it is agreed that the artisan would be motivated to look for effects of hedgehog proteins in the adult nervous system, the artisan would be required to perform extensive research and investigation to determine what cell types were amenable to manipulation with sonic hedgehog. Further, Miao et al., J. Neuroscience, 17(15)5891-5899, 1997 state that "there is no direct correlation between the neuron phenotypes induced by Shh and those supported by Shh in a trophic manner", see col 1 of page 5898. Thus, the particular teachings in the specification regarding embryonic expression

of hedgehog and manipulation of embryonic tissues could not be expected to provide the artisan with the knowledge required to manipulate adult tissues.

Additionally, the claims encompass an almost limitless number of polypeptides that comprise a portion of SEQ ID NO: 8, 11, 12, or 13, or comprise variants or portions of variants having a recited degree of identity to SEQ ID NO: 8, 11, 12, or 13. The specification sets forth that variants and portions can be used in the claimed methods, however, the specification does not provide sufficient guidance as to which of these variants and portions can actually be used to practice the claimed invention (see page 26 for example).

One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a polypeptide of SEQ ID NO: 8, 11, 12, or 13, and through trial and error experimentation is left to determine when a polypeptide is obtained that could used to promote neural cell growth, differentiation and/or survival. Such extensive random trial and error experimentation is considered undue.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative

substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2. Guo-HH et al. PNAS 101(25)9205-9210, 2004, recently reviewed the art and conducted an extensive study on the effect of amino acid substitution on the functionality of a wide variety of proteins and found that on average a single amino acid substitution had a 34% chance inactivating the functionality of the protein, see the Abstract. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants or portions that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the almost limitless number of variants and portions required by the claims and screen same for activity, and to determine which, if any adult neural cells would respond to such, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention,

the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the lack of information regarding adult neural cell responses to hedgehog proteins, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues that only in vivo methods are presently being examined. This argument has been fully considered but not deemed persuasive. The claims are not so limited and must be given their broadest reasonable interpretation.

Applicant argues that lack of expression of hedgehog in adult tissues in not required for that tissue to be sensitive to signaling by hedgehog. This argument has been fully considered but not deemed persuasive. The specification provides only speculation that certain hedgehog polypeptides could be used in adult tissues but provides the skilled artisan with only an invitation to try to find such tissues. The specification provides no practical help in this regard because the specification indicates that sonic hedgehog proteins have not been found to in adult tissues, at all, and that other hedgehog proteins have been found in the adult but only in the liver and the kidney (see page 110). One of skill in the art would therefore expect that adult neural tissues would not be responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Additionally, Applicant admits that the specification does not provide any information about patched expression in the adult either.

Applicant argues that lack of expression of the protein in the adult would not be construed by the artisan as evidence that the protein would not be useful, and that many compounds that are not endogenously expressed are known to be useful. This argument has been

fully considered but not deemed persuasive. While the skilled artisan would be motivated to look for effects of hedgehog proteins in the adult, as is evidenced by the post-filing date research on the subject, an invitation to perform that research does not constitute an enabling disclosure to use the polypeptides in any particular way in adult tissues.

Applicant's post filing date references as well as the Declarations by Dudek and Rubin have been thoroughly considered but not deemed persuasive. The very generalized speculation given in the specification about adult tissues is simply an invitation to begin further specific research. "Tossing out the mere germ of an idea does not constitute enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech, Inc. v. Novo Nordisk Inc., 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997).

Applicant argues specification clearly contemplates treatment of specific adult disorders and thus there is no basis for the examiner's assertion that one of skill in the art would need to perform undue experimentation to determine which of the multitude of adult neural cells is responsive to sonic hedgehog. This argument has been fully considered but not deemed persuasive. The specification simply provides the speculation that adult cells would respond to hedgehog polypeptides (e.g. page 63, lines 12-32). The specification suggests/speculates that hedgehog polypeptides might be active in a multitude of neurologic systems and cell types (e.g. pages 63-66). In fact, most, if not all, aspects of neurobiology appear to be encompassed by the suggestions put forth in the specification. The highly skilled artisan would thus appreciate that the contemplations of the specification amount to no more than an invitation to begin a research

plan to try to find areas of the adult nervous system that could be manipulated with hedgehog polypeptides, and then to try to find useful ways to manipulate such areas.

Applicant provides a multitude of examples wherein one species of hedgehog protein is effective in another species (pg 13), and concludes that hedgehog signaling is tolerant to some variation in the sequence of the hedgehog protein. This argument has been fully considered but not deemed persuasive. Regarding the concept of signaling being tolerant to sequence variation, there is variation between the naturally occurring sonic hedgehog proteins, referred to in Applicant's examples; yet this variation has occurred under the constraint of over 100 million years of selective pressure during the evolution of these species. These differences have arisen through random mutation, and those that did not function have been eliminated. The specification has provided little more than this strategy of evolution to guide the artisan in the construction of mutants that will function as required. The artisan is simply invited to embark on an essentially random trial and error process of experimentation wherein amino acids are substituted/added/deleted from the parent sequence and then assayed for activity to try to find variants that work. Third, the claims stipulate that the protein be required to have some effect on neuronal and glial cells, yet the specification has not provided a rapid assay such that the artisan would expected that screening for variants would be routine. Fourth, the task of assaying the mutants for function is complicated by the fact that the specification has failed to teach exactly what function should be expected in adult tissues. Thus, the extensive experimentation required to make and test the genus of mutants encompassed by the claims is unduly burdensome.

Applicant's arguments regarding the number of inoperable embodiments that are allowed to be in a claim are unpersuasive because the issue is that the specification has failed to teach how to make operable embodiments without undue experimentation.

Claims 1-3, 5, 6, 11-13, 23-26, 42-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As discussed above, regarding claims 1-3, 5, 6, 11-13, 23-26, 42-56 there is no description of methods of promoting growth, differentiation, or survival of adult neural cells, yet the claims encompass such and are contemplated in the specification.

To determine whether there is correspondence between the generic invention of the claims and the written description, is necessary to determine whether the description conveys to one skilled in the relevant art that applicant was in possession of the claimed genus at the time the application was filed. To this end, it is appropriate to inquire whether a number of species representative of the genus are described in complete structural terms or, alternatively, with reference to other identifying characteristics, *e.g.*, partial structure, chemical properties, functional properties, *etc.* What constitutes a "representative number" of species for any given genus depends in part on whether the level of skill in the art, the teachings in the disclosure, or teachings in the prior art establish predictability as to the structural properties characteristic of the genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The description of growth, differentiation, or survival promoting activity of hedgehog proteins on embryonic chicken tissues does not support the claimed genera of methods that would not be expected to behave the same way, see above. Thus the skilled artisan would not recognize that applicant was in possession of the genera of methods claimed in claims 1-3, 5, 6, 11-13, 23-26, 42-56. Thus the claims do not meet the written description requirement of 35 U.S.C. 112, first paragraph.

Applicant argues that the specification specifically contemplates the treatment of adult neural cells. This argument has been fully considered but not deemed persuasive. As discussed above, the specification suggests/speculates that hedgehog polypeptides might be active in a multitude of neurologic systems and cell types (e.g. pages 63-66). In fact, most, if not all, aspects of neurobiology appear to be encompassed by the suggestions put forth in the specification. The highly skilled artisan would thus appreciate that the contemplations of the specification amount to no more than an invitation to begin a research plan to try to find areas of the adult nervous system that could be manipulated with hedgehog polypeptides, and then to try to find useful ways to manipulate such areas. Thus one skilled in the art would not appreciate

that applicant was in possession of specific methods directed to specific neural cell types that are required to practice, and be in possession of, the claimed invention.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841. Official papers filed by fax should be directed to **571-273-8300**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

August 21, 2007

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646